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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/557,796	04/25/00	HOCH J	252/123

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EXAMINER	
LACOURCIERE, K	
ART UNIT	**PAPER NUMBER**
1635	10
DATE MAILED:	05/09/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/557,796	HOCH ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *72-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *72-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

FILE

DETAILED ACTION

Information Disclosure Statement

Reference BH on PTO form 1449 (filed 04-25-00) has not been considered because the reference is in Japanese and no English translation was provided.

References BS, BT, AO, AQ and AS on PTO form 1449 (filed Feb 18, 1999) were only considered for the information contained in the Table of Contents, as only the table of contents was provided.

Priority

1. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

It is noted that Applicant requested that the specification be amended to include a priority statement (in the transmittal letter filed 04-25-00), however, there was no indication as to where the statement should be inserted and whether Applicants intend the underlining to be included in the specification if the application should issue as a patent, so the amendment could not be entered.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 80 and 93 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 80 and 93 are indefinite due to the recitation "said cell is a bacteria." Since a bacteria and a cell are not really equivalent, it is suggested that the phrase be amended to read "said cell is a bacterial cell."

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 75-79, 82-85 and 88-92 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 75-79, 82-85 and 88-92 are drawn to nucleic acids comprising a yiaJ sequence, cells comprising nucleic acids comprising a yiaJ sequence, methods which utilize a yiaJ nucleic acid or protein and methods which utilize a promoter sequence bound by yiaJ protein.

The specification discloses SEQ ID NO: 1 and 19 which corresponds to the genomic DNA encoding the klebsiella oxytoca species of yiaJ (SEQ ID NO:1) and the full klebsiella oxytoca yia operon (SEQ ID NO: 19, which comprises SEQ ID NO:1) and further discloses the sequence of the E. coli yiaJ nucleic acid was known in the prior art. The specification does not disclose sequence of any promoter to which yiaJ protein binds. SEQ ID NO: 1 and 19 and the E. coli yiaJ meet the written description provisions of 35 USC 112, first paragraph. However, claims 75-79, 82-85 and 88-92 are directed to encompass nucleic acids and methods which utilize corresponding nucleic acid sequences and proteins from other species, as well as a promoter sequence which has not been described for even one species. None of these sequences meet the written description provision of 35 USC 112, first paragraph. Claims 75-79, 82-85 and 88-92 are drawn to a broad genus of sequences (yiaJ nucleic acids and proteins and promoters), but the specification discloses only two species of this genus and none of the species of the claimed genus in the case of the yiaJ binding promoter. These species would not be representative of the claimed genus, such that one skilled in the art would recognize that the Applicant was in possession of the claimed genus. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO: 1, 19 and the E. coli yiaJ, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins utilized in the claimed methods, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must

clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

Therefore, only SEQ ID NO: 1, 19 and the E. coli yiaJ, but not the full breadth of the claim (and nucleic acids, proteins and promoters utilized in the claimed methods) meets the

written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

6. Claims 72-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of detecting the presence of some compounds using the claimed methods, does not reasonably provide enablement for methods of detecting the presence, absence and amount of generally any compound using the claimed methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims are drawn very broadly to methods of detecting the presence absence or amount of generally any compound in a sample by contacting a cell with the sample, wherein the cell comprises one or more genes which provide a detectable signal which indicates the presence,

absence or amount of the compound, wherein the detectable signal can be growth, fluorescence, luminescence and color and wherein the compound is ascorbate.

The specification does not appear to provide any actual examples of the claimed method, however it does include a prophetic example of sensing the presence or absence of ascorbate using a cell comprising yiaJ linked to a reporter gene. The prior art provides examples wherein the claimed methods are enabled for detecting the presence of certain compounds in methods that would be encompassed in the broad methods claimed, however, the specification does not provide any guidance on what genes/promoters can be used for a particular compound and what cells to use for these particular genes/promoters. Nor does it provide any guidance on how to use any particular genes to quantitate the amount of a particular compound or any guidance on what genes and cells would be sensitive enough to determine the true absence of a compound or what genes would be selective to reliably detect the presence absence or amount of one particular compound.

The specification does not provide any guidance to one of ordinary skill in the art to detect the presence, absence or amount of virtually any compound using the claimed methods of detection. The specification does not provide adequate guidance on what genes in what cells would provide a detectable signal in response to what compounds, how to quantitate the amount of a particular compound based on a particular signal, what sensitivity particular signals have in response to an amount of a signal and what particular genes will provide a detectable "growth" signal in response to particular compounds. In particular, it seems highly unlikely that the claimed

methods of detection are sensitive enough to reliably determine the complete absence of a particular compound. For example, to provide a detectable signal from an inducible gene, or to allow growth, a compound may be present in a sample at a concentration too low to induce or to provide an essential nutrient. The result would erroneously indicate the "absence" of a compound. Further, the specification has not provided any guidance on how to quantitate the amount of any compound based on a signal. In particular, growth of a cell would not predictably correlate with the amount of a compound, once a required threshold is reached the cell may grow, but there would not be any way to quantitate beyond whether the compound is in an amount above or below the threshold. The specification has not provided any information or guidance on what the threshold amount for any particular compound is.

The specification provides a prophetic example wherein yiaJ could be used in cells as a "biosensor" for ascorbate. The specification, however, has not provided any guidance to suggest that yiaJ is actually bound and regulated by ascorbate. There is no evidence to suggest that yiaJ is actually an ascorbate "biosensor". The specification has not provided any guidance for even this one disclosed specific embodiment on how to quantitate the amount of ascorbate in a sample, whether the absence of ascorbate can be detected and whether or not growth correlates with the presence, absence or amount of ascorbate.

To practice the claimed methods of detection, one skilled in the art would need to undergo undue trial and error experimentation. This experimentation would include the determination of what compounds can be selectively detected by a particular gene or genes, how to quantitate the

amount of any particular compound, whether the claimed method is sensitive enough to detect the absence of any compound, whether of not yiaJ is actually regulated by ascorbate and, if not, what genes can be used for ascorbate detection and how to correlate growth with the amount of a particular compound. This trial and error experimentation is particularly undue given the broad scope claimed. The lack of guidance provided by the specification would require that the skilled artisan determine these factors de novo, through undue trial and error experimentation, beyond the teaching of the instant specification.

7. Claims 75-79, 82-85 and 88-92 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed methods using SEQ ID NO:19 or the E.coli yiaK-S operon, does not reasonably provide enablement for the claimed methods using any yiaJ nucleic acid or methods utilizing a yiaJ protein or a yiaJ binding promoter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 75-79, 82-85 and 88-92 are drawn to nucleic acids comprising a yiaJ sequence, cells comprising nucleic acids comprising a yiaJ sequence, methods which utilize a yiaJ nucleic acid or protein and methods which utilize a promoter sequence bound by yiaJ protein. These methods include methods wherein yiaJ is expressed and provides a detectable signal in response to the presence, absence or amount of a test compound or wherein yiaJ protein binds to a promoter and regulates the expression of a reporter gene.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claimed methods, nucleic acid constructs and cells comprising said nucleic acid constructs are not fully enabled because one skilled in the art would not know how to use the claimed nucleic acid constructs or cells comprising such, nor would they be able to practice the claimed methods because the function of the nucleic acids in the claimed methods is not known, therefore, one skilled in the art would not know what (if any) detectable signal is generated by these nucleic acids or if the yiaJ protein binds to a promoter in a manner that regulates a reporter gene. The claimed methods of detection are enabled wherein the one or more genes encodes the full Klebsiella oxytoca yia operon (SEQ ID NO:19), which does have a disclosed function and would not require undue experimentation to use as a unit. Further, the claimed methods of detection are enabled for the E.coli full yiaS-K, which has been disclosed in the instant specification and taught in the art. The claimed nucleic acid constructs (and cells comprising such), which comprise a reporter gene in addition to a yiaJ sequence, may function as a reporter gene, but one skilled in the art would not know how to use the specifically claimed constructs (or cells comprising such) since this function is generic to a reporter gene attached to any random sequence and is not specific to the instantly claimed constructs.

The specification discloses the yia operon of Klebsiella oxytoca (SEQ ID NO:19), which comprises an open reading frame called yiaJ. The specification provides examples wherein the ability of Klebsiella oxytoca to utilize ascorbic acid as a sole carbon source is knocked out by transposon interruption of the operon identified by SEQ ID NO:19. Further, an example is provided wherein the same operon is placed under control of the lac promoter within Klebsiella oxytoca and the resultant strain can only utilize ascorbic acid as a sole carbon source when induced with IPTG, demonstrating a function for the full operon as conferring the ability to utilize ascorbic acid. Based on sequence homology with the E. coli yiaS-K operon, the specification asserts yiaJ (SEQ ID NO: 1) as the transcriptional regulator of the Klebsiella oxytoca yiaS-K operon, however, the specification has not provided any evidence that would suggest that SEQ ID NO:1 encodes a transcriptional regulator, nor does it provide any evidence that yiaJ (SEQ ID NO:1) binds to a promoter sequence, or what the promoter sequence is. The specification does not provide any reliable information on the function of yiaJ (SEQ ID NO:1) or what detectable signal yiaJ (SEQ ID NO:1) would generate. The specification provides a utility for SEQ ID NO:19 (which comprises a yiaJ sequence), as conferring the ability to utilize ascorbic acid as a sole carbon source, which would also provide a detectable signal for the claimed methods. The specification has not demonstrated any open reading frame within SEQ ID NO:19, including yiaJ (SEQ ID NO:1), maintains that function or has any other particular function. Similarly, the prior art discloses the yiaS-K operon of E. coli (which comprises a yiaJ sequence), which functions to

confer the ability to utilize L-lyxose and further discloses a yiaJ nucleic acid which behaves as a transcriptional regulator of the E. coli yiaS-k operon.

One skilled in the art would not be able to determine the function of other nucleotides in other organisms, including Klebsiella oxytoca, based on homology with the sequence of the yiaS-K operon or yiaJ sequence of E.coli because, absent factual evidence, a percentage sequence similarity of less than 100 % is not deemed to reasonably support to one skilled in the art whether the biochemical activity of the claimed subject matter would be the same as that of such a similar known biomolecule. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding utility and/or enablement.

In order to use the claimed nucleic acid constructs or practice the claimed methods, one skilled in the art would need to undergo undue trial and error experimentation, beyond the teachings of the instant specification. Such undue experimentation would include the determination of the function (if any) of a yiaJ nucleic acid and whether or not a yiaJ nucleic acid generates a detectable signal, as well as what that signal is. Further, it would require the determination of whether or not yiaJ binds to a promoter in a manner that regulates the expression

of a reporter gene, what the promoter sequence is, and what compounds (if any) regulate yiaJ binding to the promoter. Therefore, at the time the instant invention was made, one skilled in the art would not be able to practice the claimed invention over the full scope claimed without undue trial and error experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 82, 83 and 84 are rejected under 35 U.S.C. 102(a) as being anticipated by Badía et al.(reference AK on PTO form 1449, filed 04-25-00).

8. Badía et al. disclose a nucleic acid encoding an E.coli yiaJ and a CAT reporter gene transcriptionally linked to said reporter gene, and further disclose cells comprising this nucleic acid. The intended use language of claim 85 is noted, however, the intended use does not

materially change the claimed recombinant cell. Therefore, Badía et al. anticipates claims 82, 83 and 84.

9. Claims 72, 74, 80, 86, 87 and 93 are rejected under 35 U.S.C. 102(a) as being anticipated by Applegate et al. (reference AJ on PTO form 1449, filed 04-25-00).

Applegate et al. disclose a method for detecting benzene, toluene, ethylbenzene and xylene using a bacterial strain which comprises genes which produces luminescence in response to the presence of any of these compounds. Therefore, Applegate et al. anticipates claims 72, 74, 80, 86, 87 and 93.

10. Claims 72, 74, 80, 86, 87 and 93 are rejected under 35 U.S.C. 102(b) as being anticipated by Selifonova et al. (reference BV on PTO form 1449, filed 04-25-00).

Selifonova et al. disclose a method of detecting certain hydrophobic pollutants using a bacterial strains which comprises genes which produce a luminescent signal in response to the presence of these compounds. Therefore, Selifonova et al. anticipates claims 72, 74, 80, 86, 87 and 93.

11. Claims 72, 74, 80, 81, 86, 87, 93 and 94 are rejected under 35 U.S.C. 102(e) as being anticipated by Trias et al.

Trias et al. disclose and claim methods for the detection of the presence of a non-tetracycline-specific efflux pump inhibitor using bacterial cells which produce the signal of inhibited growth in the presence of said inhibitor. Trias et al. disclose and claim the specific embodiment wherein the bacterial cell is Klebsiella oxytoca. Therefore, Trias et al. anticipates claims 72, 74, 80, 81, 86, 87, 93 and 94.

Claim Objections

Claim 73 is objected to due to its dependence on a rejected claim.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at (703) 308-0447. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SEAN McGARRY
PRIMARY EXAMINER
TC 1600

Karen A. Lacourciere

May 7, 2001